Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	26	Huntington.ti.	USPAT; EPO	OR	OFF	2005/05/10 14:49
L2	3935	hayes.xp.	USPAT; EPO	OR	OFF	2005/05/10 15:21
L3	0	l1 and l2	USPAT; EPO	OR	OFF	2005/05/10 14:49
L4	0	hayes-robert.xp.	USPAT; EPO	OR	OFF	2005/05/10 14:53
L5	0	l2 and (huntington near5 protein)	USPAT; EPO	OR	OFF	2005/05/10 15:24
L6	19	l2 and huntington	USPAT; EPO	OR	ON	2005/05/10 14:54
L7	1174	hayes.xa.	USPAT; EPO	OR	OFF	2005/05/10 14:55
L8	47	l7 and huntington	USPAT; EPO	OR	OFF	2005/05/10 15:09
L9	14	l7 and huntington and diameter	USPAT; EPO	OR	OFF	2005/05/10 15:00
L10	103	huntington same diameter	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:03
L11	8	huntington same diameter same filament	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/05/10 15:00
L12	105	huntington and (diameter same filament)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:04
L13	50	huntington and (diameter near15 filament)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:04
L14	14	l7 and huntington and diameter	USPAT; EPO	OR	OFF	2005/05/10 15:09
L15	19	l7 and huntington and repeat	USPAT; EPO	OR	OFF	2005/05/10 15:10
L16	19	l7 and huntington and repeat and length	USPAT; EPO	OR	OFF	2005/05/10 15:10
L17	16	l7 and huntington and repeat and nm	USPAT; EPO	OR	ON	2005/05/10 15:10
L18	885	kunz.xp.	USPAT; EPO	OR	OFF	2005/05/10 15:21

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	26	Huntington.ti.	USPAT; EPO	OR	OFF	2005/05/10 14:49
L2	3935	hayes.xp.	USPAT; EPO	OR	OFF	2005/05/10 15:21
L3	0	l1 and l2	USPAT; EPO	OR	OFF	2005/05/10 14:49
L4	0	hayes-robert.xp.	USPAT; EPO	OR	OFF	2005/05/10 14:53
L5	0	l2 and (huntington near5 protein)	USPAT; EPO	OR	OFF	2005/05/10 15:24
L6	19	l2 and huntington	USPAT; EPO	OR	ON	2005/05/10 14:54
L7	1174	hayes.xa.	USPAT; EPO	OR	OFF	2005/05/10 14:55
L8	47	l7 and huntington	USPAT; EPO	OR	OFF	2005/05/10 15:09
L9	14	l7 and huntington and diameter	USPAT; EPO	OR	OFF	2005/05/10 15:00
L10	103	huntington same diameter	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:03
L11	8	huntington same diameter same filament	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/05/10 15:00
L12	105	huntington and (diameter same filament)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:04
L13	50	huntington and (diameter near15 filament)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:04
L14	14	l7 and huntington and diameter	USPAT; EPO	OR	OFF	2005/05/10 15:09
L15	19	l7 and huntington and repeat	USPAT; EPO	OR	OFF	2005/05/10 15:10
L16	19	l7 and huntington and repeat and length	USPAT; EPO	OR	OFF	2005/05/10 15:10
L17	16	l7 and huntington and repeat and nm	USPAT; EPO	OR	ON	2005/05/10 15:10
L18	885	kunz.xp.	USPAT; EPO	OR	OFF	2005/05/10 15:21

L19	25	l18 and l8	USPAT; EPO	OR	OFF	2005/05/10 15:21
L20	1	(huntington near5 protein) same filament	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:25
L21	16	huntington same filament	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:58
L22	1	huntington same filament same diameter	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:26
L23	2	(polyQ or ((poly or repeat) near3 CAG) or polyglutamine) same aggregate same diameter	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 16:00
L24	7	(polyQ or ((poly or repeat) near3 CAG) or polyglutamine) and ((aggregate or filament or neurofilament) same diameter)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 16:00

L19	25	l18 and l8	USPAT; EPO	OR	OFF	2005/05/10 15:21
L20	1	(huntington near5 protein) same filament	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:25
L21	16	huntington same filament	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:26
L22	1	huntington same filament same diameter	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2005/05/10 15:26

```
FILE 'HOME' ENTERED AT 15:31:36 ON 10 MAY 2005

=> file .meeting
'EVENTLINE' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):ignore
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                      0.21       0.21

FILE 'AGRICOLA' ENTERED AT 15:31:45 ON 10 MAY 2005

FILE 'BIOTECHNO' ENTERED AT 15:31:45 ON 10 MAY 2005
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FILE 'CONFSCI' ENTERED AT 15:31:45 ON 10 MAY 2005
COPYRIGHT (C) 2005 Cambridge Scientific Abstracts (CSA)

FILE 'HEALSAFE' ENTERED AT 15:31:45 ON 10 MAY 2005
COPYRIGHT (C) 2005 Cambridge Scientific Abstracts (CSA)


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FILE 'LIFESCI' ENTERED AT 15:31:45 ON 10 MAY 2005
COPYRIGHT (C) 2005 Cambridge Scientific Abstracts (CSA)


FILE 'MEDICONF' ENTERED AT 15:31:45 ON 10 MAY 2005
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FILE 'PASCAL' ENTERED AT 15:31:45 ON 10 MAY 2005
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=> huntington and filament and diameter
L1            0 FILE AGRICOLA
L2            0 FILE BIOTECHNO
L3            0 FILE CONFSCI
L4            0 FILE HEALSAFE
L5            0 FILE IMSDRUGCONF
L6            0 FILE LIFESCI
L7            0 FILE MEDICONF
L8            1 FILE PASCAL

TOTAL FOR ALL FILES
L9            1 HUNTINGTON AND FILAMENT AND DIAMETER

=> d 19 ibib abs total

L9    ANSWER 1 OF 1  PASCAL  COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on
      STN
ACCESSION NUMBER:         1995-0202053   PASCAL
COPYRIGHT NOTICE:         Copyright .COPYRGT. 1995 INIST-CNRS. All rights
                          reserved.
TITLE (IN ENGLISH):       The cortical neuritic pathology of Huntington
                          's disease
```

AUTHOR: JACKSON M.; GENTLEMAN S.; LENNOX G.; WARD L.; GRAY T.; RANDALL K.; MORRELL K.; LOWE J.
CORPORATE SOURCE: Univ. Nottingham medical school, Queen's medical cent., dep. neurology, Nottingham NG7 2UH, United Kingdom
SOURCE: Neuropathology and applied neurobiology, (1995), 21(1), 18-26, 39 refs.
ISSN: 0305-1846 CODEN: NANEDL
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-17534, 354000059592270030
AN 1995-0202053 PASCAL

AB We have studied the brains of 10 patients with clinically and pathologically defined **Huntington**'s disease and graded the degree of striatal pathology according to the Vonsattel grading system. Sections from nine cerebral cortical areas (Brodmann areas 8, 10, 24, 33, 28, 38, 7, 39, 18), the cerebellum, hypothalamus, medulla and caudate nucleus were stained with antibodies to ubiquitin and ubiquitin C-terminal hydrolase (PGP 9.5). Dystrophic neurites, immunoreactive with ubiquitin and PGP 9.5 were detected in all cortical areas, in layers 3, 5 and 6, of all brains studied. No dystrophic neurites were found in subcortical areas or cerebellum. Sections from cortical areas 8 and 24 from the two brains with the most and least ubiquitin-immunoreactive neurites were stained with antibodies to β-amyloid precursor protein, tau, glial fibrillary acidic protein, neurofilament protein, αB crystallin, GABA, cholecystokinin and somatostatin. The dystrophic neurites were found to also react with β-amyloid precursor protein. Electron microscopy showed the abnormal neurites to coniain granulofilamentous material. Granular deposits with a **diameter** of 40-100 nm were interspersed between randomly orientated 'fuzzy' or coated, straight or slightly curved **filaments** measuring 10-15 nm in **diameter**. These structures have not been seen in control brain and differ from age-related neuritic degeneration and neurites associated with amyloid. Immunohistochemically these structures most resemble CA 2/3 neurites seen in Lewy body disease, and, ultrastructurally, the intraneuronal filamentous inclusions in motor neuron disease. The areal density of these neurites was quantified in 20 microscopic fields in the superior frontal and anterior cingulate sections (Brodmann areas 8 and 24) and did not correlate with the Vonsattel grade, suggesting that they are an independent and possibly primary cortical pathology in **Huntington** 's disease

=> polyQ and (filament or neurofilament) and diameter
L10 0 FILE AGRICOLA
L11 0 FILE BIOTECHNO
L12 0 FILE CONFSCI
L13 0 FILE HEALSAFE
L14 0 FILE IMSDRUGCONF
L15 0 FILE LIFESCI
L16 0 FILE MEDICONF
L17 0 FILE PASCAL

TOTAL FOR ALL FILES
L18 0 POLYQ AND (FILAMENT OR NEUROFILAMENT) AND DIAMETER

=> polyQ and diameter
L19 0 FILE AGRICOLA
L20 2 FILE BIOTECHNO

```
L21           0 FILE CONFSCI
L22           0 FILE HEALSAFE
L23           0 FILE IMSDRUGCONF
L24           1 FILE LIFESCI
L25           0 FILE MEDICONF
L26           1 FILE PASCAL

TOTAL FOR ALL FILES
L27           4 POLYQ AND DIAMETER

=> dup rem
ENTER L# LIST OR (END):l27
DUPLICATE IS NOT AVAILABLE IN 'IMSDRUGCONF, MEDICONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L27
L28            2 DUP REM L27 (2 DUPLICATES REMOVED)

=> d l28 ibib abs total

L28   ANSWER 1 OF 2  BIOTECHNO  COPYRIGHT 2005 Elsevier Science B.V. on STN
      DUPLICATE
ACCESSION NUMBER:         2003:36389706   BIOTECHNO
TITLE:                    Aggregate formation and the impairment of long-term
                          synaptic facilitation by ectopic expression of mutant
                          huntingtin in Aplysia neurons
AUTHOR:                   Lee J.-A.; Lim C.-S.; Lee S.-H.; Kim H.; Nukina N.;
                          Kaang B.-K.
CORPORATE SOURCE:         B.-K. Kaang, Inst. of Molec. Biology and Genetics,
                          Seoul National University, San 56-1 Silim-dong,
                          Kwanak-gu, Seoul 151-742, South Korea.
                          E-mail: kaang@snu.ac.kr
SOURCE:                   Journal of Neurochemistry, (2003), 85/1 (160-169), 55
                          reference(s)
                          CODEN: JONRA0  ISSN: 0022-3042
DOCUMENT TYPE:            Journal; Article
COUNTRY:                  United Kingdom
LANGUAGE:                 English
SUMMARY LANGUAGE:         English
AN    2003:36389706   BIOTECHNO
AB    Huntington's disease (HD) is caused by an expansion of a polyglutamine (
      polyQ) tract within huntingtin (htt) protein. To examine the
      cytotoxic effects of polyQ-expanded htt, we overexpressed an
      enhanced green fluorescent protein (EGFP)-tagged N-terminal fragment of
      htt with 150 glutamine residues (Nhtt150Q-EGFP) in Aplysia neurons. A
      combined confocal and electron microscopic study showed that Aplysia
      neurons expressing Nhtt150Q-EGFP displayed numerous abnormal aggregates (
      diameter 0.5-5 μm) of filamentous structures, which were
      formed rapidly (approximately 2 h) but which were sustained for at least
      18 days in the cytoplasm. Furthermore, the overexpression of
      Nhtt150Q-EGFP in sensory cells impaired 5-hydroxytryptamine
      (5-HT)-induced long-term synaptic facilitation in sensori-motor synapses
      without affecting basal synaptic strength or short-term facilitation.
      This study demonstrates the stability of polyQ-based aggregates
      and their specific effects on long-term synaptic plasticity.

L28   ANSWER 2 OF 2  BIOTECHNO  COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER:         1999:29477959   BIOTECHNO
TITLE:                    Aggregation of truncated GST-HD exon 1 fusion proteins
                          containing normal range and expanded glutamine repeats
AUTHOR:                   Hollenbach B.; Scherzinger E.; Schweiger K.; Lurz R.;
                          Lehrach H.; Wanker E.E.
CORPORATE SOURCE:         E.E. Wanker, Max-Planck-Inst. fur Molek. Genetik,
                          Ihnestrasse 73, D-14195 Berlin, Germany.
```

E-mail: wanker@mpimg-berlin-dahlem.mpg.de
SOURCE: Philosophical Transactions of the Royal Society of London Series B Biological Sciences, (29 JUN 1999), 354/1386 (991-994), 18 reference(s)
CODEN: PTRBAE ISSN: 0962-8436
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29477959 BIOTECHNO
AB We have shown previously by electron microscopy that the purified glutathione S-transferase (GST)Huntington's disease (HD) exon 1 fusion protein with 51 glutamine residues (GST-HD51) is an oligomer, and that site-specific proteolytic cleavage of this fusion protein results in the formation of insoluble more highly ordered protein aggregates with a fibrillar or ribbon-like morphology (E. Scherzinger et al. (1997) Cell 90, 549-558). Here we report that a truncated GST-HD exon 1 fusion protein with 51 glutamine residues, which lacks the proline-rich region C-terminal to the polyglutamine (**polyQ**) tract (GST-HD51 ΔP) self-aggregates into high-molecular-mass protein aggregates without prior proteolytic cleavage. Electron micrographs of these protein aggregates revealed thread-like fibrils with a uniform **diameter** of ca. 25 nm. In contrast, proteolytic cleavage of GST-HD51ΔP resulted in the formation of numerous dusters of high-molecular-mass fibrils with a different, ribbon-like morphology. These structures were reminiscent of prion rods and β-amyloid fibrils in Alzheimer's disease. In agreement with our previous results with full-length GST-HD exon 1, the truncated fusion proteins GST-HD20ΔP and GST-HD30ΔP did not show any tendency to form more highly ordered structures, either with or without protease treatment.

=> (CAG repeat) and (neurofilament or aggregate) and (diameter or length)
L29 0 FILE AGRICOLA
L30 25 FILE BIOTECHNO
L31 0 FILE CONFSCI
L32 0 FILE HEALSAFE
L33 0 FILE IMSDRUGCONF
L34 20 FILE LIFESCI
L35 0 FILE MEDICONF
L36 12 FILE PASCAL

TOTAL FOR ALL FILES
L37 57 (CAG REPEAT) AND (NEUROFILAMENT OR AGGREGATE) AND (DIAMETER OR LENGTH)

=> 137 and diameter
L38 0 FILE AGRICOLA
L39 0 FILE BIOTECHNO
L40 0 FILE CONFSCI
L41 0 FILE HEALSAFE
L42 0 FILE IMSDRUGCONF
L43 0 FILE LIFESCI
L44 0 FILE MEDICONF
L45 0 FILE PASCAL

TOTAL FOR ALL FILES
L46 0 L37 AND DIAMETER

=> 137 and length
L47 0 FILE AGRICOLA
L48 25 FILE BIOTECHNO
L49 0 FILE CONFSCI

```
L50           0 FILE HEALSAFE
L51           0 FILE IMSDRUGCONF
L52          20 FILE LIFESCI
L53           0 FILE MEDICONF
L54          12 FILE PASCAL

TOTAL FOR ALL FILES
L55          57 L37 AND LENGTH

=> 137 and diameter
L56           0 FILE AGRICOLA
L57           0 FILE BIOTECHNO
L58           0 FILE CONFSCI
L59           0 FILE HEALSAFE
L60           0 FILE IMSDRUGCONF
L61           0 FILE LIFESCI
L62           0 FILE MEDICONF
L63           0 FILE PASCAL

TOTAL FOR ALL FILES
L64           0 L37 AND DIAMETER

=>  dup rem
ENTER L# LIST OR (END):137
DUPLICATE IS NOT AVAILABLE IN 'IMSDRUGCONF, MEDICONF'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L37
L65          30 DUP REM L37 (27 DUPLICATES REMOVED)

=> 165 and polyglutamine
L66           0 S L65
L67           0 FILE AGRICOLA
L68          25 S L65
L69          24 FILE BIOTECHNO
L70           0 S L65
L71           0 FILE CONFSCI
L72           0 S L65
L73           0 FILE HEALSAFE
L74           0 S L65
L75           0 FILE IMSDRUGCONF
L76           5 S L65
L77           5 FILE LIFESCI
L78           0 S L65
L79           0 FILE MEDICONF
L80           0 S L65
L81           0 FILE PASCAL

TOTAL FOR ALL FILES
L82          29 L65 AND POLYGLUTAMINE

=> d l82 ibib abs total

L82   ANSWER 1 OF 29  BIOTECHNO  COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER:        2002:37465753   BIOTECHNO
TITLE:                   Lentiviral-Mediated Delivery of Mutant Huntingtin in
                         the Striatum of Rats Induces a Selective
                         Neuropathology Modulated by Polyglutamine
                         Repeat Size, Huntingtin Expression Levels, and Protein
                         Length
AUTHOR:                  De Almeida L.P.; Ross C.A.; Zala D.; Aebischer P.;
                         Deglon N.
CORPORATE SOURCE:        Dr. N. Deglon, Institute of Neuroscience, Swiss Fed.
                         Inst. Technol. Lausanne, Building SG-AAI, 1015
```

Lausanne, Switzerland.
E-mail: nicole.deglon@epfl.ch
SOURCE: Journal of Neuroscience, (01 MAY 2002), 22/9 (3473-3483), 70 reference(s)
CODEN: JNRSDS ISSN: 0270-6474
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2002:37465753 BIOTECHNO
AB A new strategy based on lentiviral-mediated delivery of mutant huntingtin (htt) was used to create a genetic model of Huntington's disease (HD) in rats and to assess the relative contribution of **polyglutamine** (**CAG**) **repeat** size, htt expression levels, and protein **length** on the onset and specificity of the pathology. Lentiviral vectors coding for the first 171, 853, and 1520 amino acids of wild-type (19 CAG) or mutant htt (44, 66, and 82 CAG) driven by either the phosphoglycerate kinase 1 (PGK) or the cytomegalovirus (CMV) promoters were injected in rat striatum. A progressive pathology characterized by sequential appearance of ubiquitinated htt **aggregates**, loss of dopamine- and cAMP-regulated phosphoprotein of 32 kDa staining, and cell death was observed over 6 months with mutant htt. Earlier onset and more severe pathology occurred with shorter fragments, longer **CAG repeats**, and higher expression levels. Interestingly, the **aggregates** were predominantly located in the nucleus of PGK-htt171-injected rats, whereas they were present in both the nucleus and processes of CMV-htt171-injected animals expressing lower transgene levels. Finally, a selective sparing of interneurons was observed in animals injected with vectors expressing mutant htt. These data demonstrate that lentiviral-mediated expression of mutant htt provides a robust in vivo genetic model for selective neural degeneration that will facilitate future studies on the pathogenesis of cell death and experimental therapeutics for HD.

L82 ANSWER 2 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:37391345 BIOTECHNO
TITLE: Intra- and Intermolecular β-Pleated Sheet Formation in Glutamine-repeat Inserted Myoglobin as a Model for **Polyglutamine** Diseases
AUTHOR: Tanaka M.; Morishima I.; Akagi T.; Hashikawa T.; Nukina N.
CORPORATE SOURCE: N. Nukina, Laboratory for CAG Repeat Diseases, RIKEN Brain Science Institute, 2-1 Hirosawa, Wakoshi, Saitama 351-0198, Japan.
E-mail: nukina@brain.riken.go.jp
SOURCE: Journal of Biological Chemistry, (30 NOV 2001), 276/48 (45470-45475), 26 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:37391345 BIOTECHNO
AB An aberrant structure of the expanded **polyglutamine** might be involved in the formation of **aggregates** in **CAG repeat** diseases. To elucidate structural properties of the expanded **polyglutamine**, we prepared sperm whale myoglobin (Mb) mutants, in which 12, 28, 35, and 50 repeats of glutamine were inserted at the corner between the C and D helices (Gln.sub.1.sub.2, Gln.sub.2.sub.8, Gln .sub.3.sub.5, and Gln.sub.5.sub.0, respectively). Circular dichroism and IR spectroscopies showed that the expanded **polyglutamine**, which was recognized by the monoclonal antibody 1C2 in Gln.sub.2.sub.8, Gln.sub.3.sub.5, and Gln .sub.5.sub.0 Mb forms an

antiparallel β-pleated sheet structure. Gln .sub.5.sub.0 Mb **aggregates** were found to comprise an intermolecular antiparallel β-pleated sheet. Fluorescence together with .sup.1H NMR spectra revealed partial unfolding of the protein surface in Gln.sub.3.sub.5 and Gln.sub.5.sub.0 Mb, although the structural changes in the protein core were rather small. The present results indicate that the fluctuating β-pleated sheet of the expanded **polyglutamine** exposed on the protein surface facilitates the formation of **aggregates** through intermolecular interactions. The present study has first established and characterized structural properties of a molecular model for **polyglutamine** diseases in which various **lengths** of **polyglutamine** including a pathologically expanded glutamine repeat were inserted into a structurally known protein.

L82 ANSWER 3 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2002:35331822 BIOTECHNO
TITLE: Aggregated **polyglutamine** peptides delivered to nuclei are toxic to mammalian cells
AUTHOR: Yang W.; Dunlap J.R.; Andrews R.B.; Wetzel R.
CORPORATE SOURCE: R. Wetzel, Graduate School of Medicine, University of Tennessee Medical Ctr., 1924 Alcoa Highway, Knoxville, TN 37920, United States.
E-mail: rwetzel@mc.utmck.edu
SOURCE: Human Molecular Genetics, (01 NOV 2002), 11/23 (2905-2917), 51 reference(s)
CODEN: HMGEE5 ISSN: 0964-6906
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2002:35331822 BIOTECHNO
AB A number of observations point to the aggregation of expanded **polyglutamine** [poly(Q)]-containing proteins as playing a central role in the etiology of Huntington's disease (HD) and other expanded **CAG-repeat** diseases. Transfected cell and transgenic animal models provide some of this support, but irrefutable data on the cytotoxicity of poly(Q) **aggregates** is lacking. This may be due in part to difficulties in observing all aggregated states in these models, and in part to the inability to conclusively rule out the role of monomeric states of the poly(Q) protein. To address these questions, we produced **aggregates** of simple poly(Q) peptides in vitro and introduced them to mammalian cells in culture. We find that Cos-7 and PC-12 cells in culture readily take up **aggregates** of chemically synthesized poly(Q) peptides. Simple poly(Q) **aggregates** are localized to the cytoplasm and have little impact on cell viability. **Aggregates** of poly(Q) peptides containing a nuclear localization signal, however, are localized to nuclei and lead to dramatic cell death. Amyloid fibrils of a non-poly(Q) peptide are non-toxic, whether localized to the cytoplasm or nucleus. Nuclear localization of an **aggregate** of a short, Q.sub.2.sub.0, poly(Q) peptide is just as toxic as that of a long poly(Q) peptide, supporting the notion that the influence of poly(Q) repeat **length** on disease risk and age of onset is at the level of aggregation efficiency. The results support a direct role for poly(Q) **aggregates** in HD-related neurotoxicity.

L82 ANSWER 4 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2002:34994493 BIOTECHNO
TITLE: Huntington's disease age-of-onset linked to **polyglutamine** aggregation nucleation
AUTHOR: Chen S.; Ferrone F.A.; Wetzel R.
CORPORATE SOURCE: R. Wetzel, Graduate School of Medicine, Univ. of Tennessee Medical Center, 1924 Alcoa Highway, Knoxville, TN 37920, United States.

E-mail: rwetzel@mc.utmck.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (03 SEP 2002), 99/18 (11884-11889), 33 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2002:34994493 BIOTECHNO
AB In Huntington's Disease and related expanded **CAG repeat** diseases, a **polyglutamine** [poly(Gln)] sequence containing 36 repeats in the corresponding disease protein is benign, whereas a sequence with only 2-3 additional glutamines is associated with disease risk. Above this threshold range, longer repeat **lengths** are associated with earlier ages-of-onset. To investigate the biophysical basis of these effects, we studied the in vitro aggregation kinetics of a series of poly(Gln) peptides. We find that poly(Gln) peptides in solution at 37°C undergo a random coil to β-sheet transition with kinetics superimposable on their aggregation kinetics, suggesting the absence of soluble, β-sheet-rich intermediates in the aggregation process. Details of the time course of **aggregate** growth confirm that poly(Gln) aggregation occurs by nucleated growth polymerization. Surprisingly, however, and in contrast to conventional models of nucleated growth polymerization of proteins, we find that the aggregation nucleus is a monomer. That is, nucleation of poly(Gln) aggregation corresponds to an unfavorable protein folding reaction. Using parameters derived from the kinetic analysis, we estimate the difference in the free energy of nucleus formation between benign and pathological **length** poly(Gln)s to be less than 1 kcal/mol. We also use the kinetic parameters to calculate predicted aggregation curves for very low concentrations of poly(Gln) that might obtain in the cell. The repeat-**length**-dependent differences in predicted aggregation lag times are in the same range as the **length**-dependent age-of-onset differences in Huntington's disease, suggesting that the biophysics of poly(Gln) aggregation nucleation may play a major role in determining disease onset.

L82 ANSWER 5 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:33062345 BIOTECHNO
TITLE: **Polyglutamine** tract expansion of the androgen receptor in a motoneuronal model of spinal and bulbar muscular atrophy
AUTHOR: Piccioni F.; Simeoni S.; Andriola I.; Armatura E.; Bassanini S.; Pozzi P.; Poletti A.
CORPORATE SOURCE: A. Poletti, Istituto di Endocrinologia, Universita degli Studi di Milano, Via Balzaretti 9, 20133 Milano, Italy.
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SOURCE: Brain Research Bulletin, (01 NOV 2001), 56/3-4 (215-220), 66 reference(s)
CODEN: BRBUDU ISSN: 0361-9230
PUBLISHER ITEM IDENT.: S0361923001006529
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:33062345 BIOTECHNO
AB Spinobulbar muscular atrophy (SBMA) is a late-onset disorder characterized by progressive muscle loss, degeneration of motoneurons in the spinal cord and brainstem, and partial androgen insensitivity. SBMA is directly correlated with the expansion of **CAG repeats** encoding a **polyglutamine** tract (polyQ) of

extended **length**. The identification of polyQ expansion in SBMA led to the discovery of an entire class of neurodegenerative disorders. In fact, at least eight different diseases, including Huntington's disease, share a common molecular mechanism involving an expansion of a polyQ tract within different proteins. The elongated polyQ tract causes a toxic gain of function in the mutant protein and is associated with the formation of intracellular **aggregates**, whose pathogenetic role has not been fully established yet. Our observations in a motoneuron cell line (NSC34), indicate that the expression of the androgen receptor (AR) carrying the elongated polyQ tract (AR-Q48) has a toxic effect in **aggregate**-independent manner. In fact, in basal condition, AR-Q48 shows a cytoplasmic diffuse distribution, yet it reduces the viability of transfected NSC34. In contrast, testosterone treatment, while inducing aggregation of the mutant AR, also increases cell viability. **Aggregates** in NSC34 are localized mainly in the perinuclear region and occasionally in the neuropil, whereas no nuclear **aggregate** has ever been found. Further observations of the minor subset of cells showing neuropil **aggregates**, reveal an alteration of the neurite morphology, suggesting a different role of the two types of cytoplasmic **aggregates**. Copyright .COPYRGT. 2001 Elsevier Science Inc.

L82 ANSWER 6 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:33010672 BIOTECHNO
TITLE: Amino acid sequences flanking **polyglutamine** stretches influence their potential for **aggregate** formation
AUTHOR: Nozaki K.; Onodera O.; Takano H.; Tsuji S.
CORPORATE SOURCE: O. Onodera, Department of Neurology, Brain Research Institute, Niigata University, 1-757 Asahimachi-dori, Niigata 951-8585, Japan.
SOURCE: NeuroReport, (29 OCT 2001), 12/15 (3357-3364), 16 reference(s)
CODEN: NERPEZ ISSN: 0959-4965
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:33010672 BIOTECHNO
AB Expanded **polyglutamine** stretches have been shown to form **aggregates** and to be toxic to cells. In this study, we hypothesized that amino acid sequences flanking the **polyglutamine** stretches influence the **aggregate** formation potential of these stretches. Green fluorescent protein (GFP) fusion proteins containing glutamine repeats of various **lengths** and a fixed number of flanking amino acids of ataxin-2, huntingtin, dentatorubral-pallidoluysian atrophy protein (DRPLAP) or ataxin-3 were transiently expressed in COS-7 cells. The **aggregate** formation potential of ataxin-2 and DRPLAP increased in a **CAG-repeat-length**-dependent manner, with a threshold between 34 and 36. Truncated ataxin-2-Q56-GFP and truncated huntingtin-Q56-GFP showed a significantly higher **aggregate** formation potential than truncated DRPLAP-Q56-GFP or truncated ataxin-3-Q56-GFP. These results are in agreement with the clinical observation that ages of disease onset in patients with spinocerebellar ataxia type 2 or Huntington's disease are lower than those in patients with DRPLA or Machado-Joseph disease having expanded **CAG repeats** of the same **length**. Furthermore, mutagenesis of the flanking sequence of ataxin-2 markedly reduced its **aggregate** formation potential. These results indicate that the amino acid sequences flanking the **polyglutamine** stretches significantly influence their **aggregate** formation potential. .COPYRGT. 2001 Lippincott Williams & Wilkins.

L82 ANSWER 7 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:32962888 BIOTECHNO
TITLE: Characterization of intracellular **aggregates** using fluorescently-tagged **polyglutamine** -expanded androgen receptor
AUTHOR: Panet-Raymond V.; Gottlieb B.; Beitel L.K.; Schipper H.; Timiansky M.; Pinsky L.; Trifiro M.A.
CORPORATE SOURCE: Dr. B. Gottlieb, Lady Davis Inst. Medical Research, Sir M.B. Davis-Jewish Gen. Hospital, 3755 Cote-Ste-Catherine Rd., Montreal, Que. H3T 1E2, Canada.
E-mail: MC33@musica.mcgill.ca
SOURCE: Neurotoxicity Research, (2001), 3/3 (259-275), 76 reference(s)
CODEN: NURRFI ISSN: 1029-8428
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32962888 BIOTECHNO
AB Spinal bulbar muscular atrophy (SBMA) is a classic **CAG-repeat** neurodegenerative disease. It is caused by expansion of a **polyglutamine** (polyGln) tract in the androgen receptor (AR). Recent evidence has indicated a potential role for nuclear and cytoplasmic inclusions in the pathogenesis of these diseases. We have used blue and green fluorescently-tagged AR to show that both wild-type (WT) and poly-Gln-expanded full-**length** AR can form **aggregates** and that aggregation is not related to cytotoxicity. Twenty to thirty-five percent of all cell types transfected into COS cells showed aggregation containing both amino- and carboxy-terminal fluorescent tags. The **aggregates** reacted with (F39.4.1), an anti-AR antibody and with 1C2, an expanded polyGln tract antibody. Western analysis of protein extracts revealed little evidence of proteolysis although some cleavage of the fusion proteins was seen. The general caspase inhibitor, Z-DEVD-FMK, did not affect aggregation in either wild type or polyGln-expanded GFP-AR transfected cells. Surprisingly, addition of Mibolerone a synthetic androgen significantly decrease inclusion formation in both WT and polyGln-expanded AR-transfected cells. Overall, we show that both WT and polyGln expanded full-**length** AR are found in **aggregates** and that proteolysis is not a requirement for aggregation. Our results also suggest that toxicity is not related to intracellular aggregation of polyGln expanded AR.

L82 ANSWER 8 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:32899099 BIOTECHNO
TITLE: **Polyglutamine** expansions cause decreased CRE-mediated transcription and early gene expression changes prior to cell death in an inducible cell model of Hungtington's disease
AUTHOR: Wyttenbach A.; Swartz J.; Kita H.; Thykjaer T.; Carmichael J.; Bradley J.; Brown R.; Maxwell M.; Schapira A.; Orntoft T.F.; Kato K.; Rubinsztein D.C.
CORPORATE SOURCE: D.C. Rubinsztein, Wellcome Trust Ctr. Mol. Mech. Dis., Cambridge Inst. for Medical Research, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2XY, United Kingdom.
E-mail: dcr1000@cus.cam.ac.uk
SOURCE: Human Molecular Genetics, (15 AUG 2001), 10/17 (1829-1845), 68 reference(s)
CODEN: HMGEE5 ISSN: 0964-6906
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom

LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32899099 BIOTECHNO
AB Huntington's disease (HD) is one of 10 known diseases caused by a (CAG).sub.n trinucleotide repeat expansion that is translated into an abnormally long **polyglutamine** tract. We have developed stable inducible neuronal (PC12) cell lines that express huntingtin exon 1 with varying **CAG repeat lengths** under doxycycline (dox) control. The expression of expanded repeats is associated with **aggregate** formation, caspase-dependent cell death and decreased neurite outgrowth. Post-mitotic cells expressing mutant alleles were more prone to cell death compared with identical cycling cells. To determine early metabolic changes induced by this mutation in cell models, we studied changes in gene expression after 18 h dox induction, using Affymetrix arrays, cDNA filters and adapter-tagged competitive PCR (ATAC-PCR). At this time point there were low rates of inclusion formation, no evidence of mitochondrial compromise and no excess cell death in the lines expressing expanded compared with wild-type repeats. The expression profiles suggest novel targets for the HD mutation and were compatible with impaired cAMP response element (CRE)-mediated transcription, which we confirmed using CRE-luciferase reporter assays. Reduced CRE-mediated transcription may contribute to the loss of neurite outgrowth and cell death in **polyglutamine** diseases, as these phenotypes were partially rescued by treating cells with cAMP or forskolin.

L82 ANSWER 9 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:32756978 BIOTECHNO
TITLE: A microtiter plate assay for **polyglutamine aggregate** extension
AUTHOR: Berthelier V.; Hamilton J.B.; Chen S.; Wetzel R.
CORPORATE SOURCE: R. Wetzel, Graduate School of Medicine, R221, Univ. of Tennessee Medical Center, 1924 Alcoa Highway, Knoxville, TN 37920, United States.
SOURCE: Analytical Biochemistry, (15 AUG 2001), 295/2 (227-236), 43 reference(s)
CODEN: ANBCA2 ISSN: 0003-2697
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32756978 BIOTECHNO
AB **Polyglutamine** (polyGln) **aggregates** are neuropathological markers of expanded **CAG repeat** disorders, and may also play a critical role in the development of these diseases. We have established a highly sensitive, fast, reproducible, and specific assay capable of monitoring **aggregate**-dependent deposition of **polyglutamine** peptides. This assay allows detailed studies on various aspects of aggregation kinetics, and also makes possible the detection and quantitation of low levels of "extension-competent" **aggregates**. In the simplest form of this assay, polyGln **aggregates** are made from chemically synthesized peptides and immobilized onto microplate wells. These wells are incubated for different times with low concentrations of a soluble biotinylated polyGln peptide. Europium-streptavidin complexation of the immobilized biotin, followed by time-resolved fluorescence detection of the deposited europium, allows us to calculate the rate (fmol/h) of incorporation of polyGln peptides into polyGln **aggregates**. This assay will make possible basic studies on the assembly mechanism of polyGln **aggregates** and on critical features of the reaction, such as polyGln **length** dependence. The assay also will be a valuable tool for screening and characterizing antiaggregation inhibitors. It will also be useful for detection and quantitation of aggregation-competent

polyGln **aggregates** in biological materials, which may prove to be of critical importance in understanding the disease mechanism. .COPYRGT. 2001 Academic Press.

L82 ANSWER 10 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:32735322 BIOTECHNO
TITLE: **Polyglutamine** aggregation behavior in vitro supports a recruitment mechanism of cytotoxicity
AUTHOR: Chen S.; Berthelier V.; Yang W.; Wetzel R.
CORPORATE SOURCE: R. Wetzel, Graduate School of Medicine, University of Tennessee Medical Ctr., 1924 Alcoa Highway, Knoxville, TN 37920, United States.
E-mail: rwetzel@mc.utmck.edu
SOURCE: Journal of Molecular Biology, (03 AUG 2001), 311/1 (173-182), 54 reference(s)
CODEN: JMOBAK ISSN: 0022-2836
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32735322 BIOTECHNO
AB In expanded **CAG repeat** diseases such as Huntington's disease, proteins containing **polyglutamine** (poly(Gln)) sequences with repeat **lengths** of about 37 residues or more are associated with development of both disease symptoms and neuronal intranuclear inclusions (NIIs). Disease physiology in animal and cellular models does not always correlate with NII formation, however, and the mechanism by which **aggregate** formation might lead to cytotoxicity is unknown. To help evaluate various possible mechanisms, we determined the biophysical properties of a series of simple poly(Gln) peptides. The circular dichroism spectra of poly(Gln) peptides with repeat **lengths** of tive, 15, 28 and 44 residues are all nearly identical and are consistent with a high degree of random coil structure, suggesting that the **length**-dependence of disease is not related to a conformational change in the monomeric states of expanded poly(Gln) sequences. In contrast, there is a dramatic increase in both the kinetics and the thermodynamic favorability of the spontaneous formation of ordered, amyloid-like **aggregates** for poly(Gln) peptides with repeat **lengths** of greater than 37 residues. At the same time, poly(Gln) peptides with repeat **lengths** in the 15-20 residue range, despite their poor abilities to support spontaneous, self-nucleated aggregation, are capable of efficiently adding to an already-formed **aggregate**. We also find that morphologically small, finely divided **aggregates** are much more efficient at recruiting poly(Gln) peptides than are large **aggregates**, suggesting a possible explanation for why disease pathology does not always correlate with the observable NII burden. Together, these data are consistent with a model for disease pathology in which critical cellular proteins possessing poly(Gln) sequences of modest **length** become inactivated when they are recruited into **aggregates** of an expanded poly(Gln) protein. .COPYRGT. 2001 Academic Press.

L82 ANSWER 11 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:32447782 BIOTECHNO
TITLE: Altered proteasomal function due to the expression of **polyglutamine**-expanded truncated N-terminal huntingtin induces apoptosis by caspase activation through mitochondrial cytochrome c release
AUTHOR: Jana N.R.; Zemskov E.A.; Wang G.-H.; Nukina N.
CORPORATE SOURCE: N. Nukina, Laboratory for CAG Repeat Diseases, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan.
E-mail: nukina@brain.riken.go.jp

SOURCE: Human Molecular Genetics, (01 MAY 2001), 10/10 (1049-1059), 65 reference(s)
CODEN: HMGEE5 ISSN: 0964-6906
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32447782 BIOTECHNO
AB Expansion of **CAG repeats** within the coding region of target genes is the cause of several autosomal dominant neurodegenerative diseases including Huntington's disease (HD). A hallmark of HD is the proteolytic production of N-terminal fragments of huntingtin containing **polyglutamine** repeats that form ubiquitinated **aggregates** in the nucleus and cytoplasm of the affected neurons. In this study, we used an ecdysone-inducible stable mouse neuro2a cell line that expresses truncated N-terminal huntingtin (tNhtt) with different **polyglutamine length**, along with mice transgenic for HD exon 1, to demonstrate that the ubiquitin-proteasome pathway is involved in the pathogenesis of HD. Proteasomal 20S core catalytic component was redistributed to the **polyglutamine aggregates** in both the cellular and transgenic mouse models. Proteasome inhibitor dramatically increased the rate of **aggregate** formation caused by tNhtt protein with 60 glutamine (60Q) repeats, but had very little influence on **aggregate** formation by tNhtt protein with 150Q repeats. Both normal and **polyglutamine**-expanded tNhtt proteins were degraded by proteasome, but the rate of degradation was inversely proportional to the repeat **length**. The shift of the proteasomal components from the total cellular environment to the **aggregates** , as well as the comparatively slower degradation of tNhtt with longer **polyglutamine**, decreased the proteasome's availability for degrading other key target proteins, such as p53. This altered proteasomal function was associated with disrupted mitochondrial membrane potential, released cytochrome c from mitochondria into the cytosol and activated caspase-9- and caspase-3-like proteases. These results suggest that the impaired proteasomal function plays an important role in **polyglutamine** protein-induced cell death.

L82 ANSWER 12 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:32240515 BIOTECHNO
TITLE: Solubilization and disaggregation of **polyglutamine** peptides
AUTHOR: Chen S.; Wetzel R.
CORPORATE SOURCE: Dr. R. Wetzel, Graduate School of Medicine, R221 Univ. of Tennessee Med. Center, 1924 Alcoa Highway, Knoxville, TN 37920, United States.
E-mail: rwetzel@mc.utmck.edu
SOURCE: Protein Science, (2001), 10/4 (887-891), 16 reference(s)
CODEN: PRCIEI ISSN: 0961-8368
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32240515 BIOTECHNO
AB A method is described for dissolving and disaggregating chemically synthesized **polyglutamine** peptides. **Polyglutamine** peptides longer than about Q.sub.2.sub.0 have been reported to be insoluble in water, but dissolution in - and evaporation from - a mixture of trifluoroacetic acid and hexafluoroisopropanol converts **polyglutamine** peptides up to at least Q.sub.4.sub.4 to a form readily soluble in aqueous buffers. This procedure also has a dramatic effect on peptides which appear to be completely soluble in water, by removing traces of **aggregate** that seed aggregation. The

protocol makes possible solution studies - including in vitro aggregation experiments - on **polyglutamine** peptides with repeat **lengths** associated with increased risk of Huntington's Disease and other expanded **CAG repeat** diseases. It may also be useful in conducting reproducible, quantitative aggregation studies on other polypeptides.

L82 ANSWER 13 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2000:30650839 BIOTECHNO
TITLE: Bacterial and yeast chaperones reduce both **aggregate** formation and cell death in mammalian cell models of huntington's disease
AUTHOR: Carmichael J.; Chatellier J.; Woolfson A.; Milstein C.; Fersht A.R.; Rubinsztein D.C.
CORPORATE SOURCE: D.C. Rubinsztein, Department of Medical Genetics, Wellcome Trust Ctr. Mole. Mech. Dis., Cambridge Institute Medical Research, Hills Road, Cambridge CB2 2XY, United Kingdom.
E-mail: dcr1000@cus.cam.ac.uk
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (15 AUG 2000), 97/17 (9701-9705)
CODEN: PNASA6 ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:30650839 BIOTECHNO
AB Huntington's disease (HD) is an autosomal dominant neurodegenerative condition caused by expansions of more than 35 uninterrupted **CAG repeats** in exon 1 of the huntingtin gene. The **CAG repeats** in HD and the other seven known diseases caused by CAG codon expansions are translated into long **polyglutamine** tracts that confer a deleterious gain of function on the mutant proteins. Intraneuronal inclusions comprising **aggregates** of the relevant mutant proteins are found in the brains of patients with HD and related diseases. It is crucial to determine whether the formation of inclusions is directly pathogenic, because a number of studies have suggested that **aggregates** may be epiphenomena or even protective. Here, we show that fragments of the bacterial chaperone GroEL and the full-**length** yeast heat shock protein Hsp104 reduce both **aggregate** formation and cell death in mammalian cell models of HD, consistent with a causal link between aggregation and pathology.

L82 ANSWER 14 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29487393 BIOTECHNO
TITLE: Insoluble detergent-resistant **aggregates** form between pathological and nonpathological **lengths** of **polyglutamine** in mammalian cells
AUTHOR: Kazantsev A.; Preisinger E.; Dranovsky A.; Goldgaber D.; Housman D.
CORPORATE SOURCE: D. Housman, Center for Cancer Research, Massachusetts Inst. of Technology, Cambridge, MA 02139, United States.
E-mail: dhousman@mit.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (28 SEP 1999), 96/20 (11404-11409), 22 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English

SUMMARY LANGUAGE: English
AN 1999:29487393 BIOTECHNO
AB Pathological degeneration of neurons in Huntington's disease and associated nenrodegenerative disorders is directly correlated with the expansion of **CAG repeats** encoding **polyglutamines** of extended **length**. The physical properties of extended **polyglutamines** and the intracellular consequences of expression of **polyglutamine** expansion have been the object of intensive investigation. We have extended the range of **lengths** of **polyglutamine** produced by recombinant DNA methodology by constructing a library of CAG/CAA repeats coding for a range of 25-300 glutamine residues. We have investigated the subcellular localization, interaction with other **polyglutamine**-containing polypeptides, and the physical properties of aggregated forms of **polyglutamine** in the cell. Extended polyQ aggregated in the cytoplasm and was only transported to the nucleus when a strong nuclear localization signal was present. **Polyglutamine** below pathological **lengths** could be captured in **aggregates** and transported to ectopic cell locations. The CREB-binding protein (CBP), containing a homopolymeric stretch of 19 glutamines, was likewise found to coaggregate in a **polyglutamine**-dependent manner, suggesting that pathology in **polyglutamine** disease may result from cellular depletion of normal proteins containing **polyglutamine**. We have observed a striking detergent resistance in **aggregates** produced from **polyglutamine** of pathological **length**. This observation has led to the development of a fluorescence-based assay exploiting the detergent resistance of **polyglutamine aggregates** that should facilitate high-throughput screening for agents that suppress **polyglutamine** aggregation in cells.

L82 ANSWER 15 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29477971 BIOTECHNO
TITLE: Progress in pathogenesis studies of spinocerebellar ataxia type 1
AUTHOR: Cummings C.J.; Orr H.T.; Zoghbi H.Y.
CORPORATE SOURCE: H.Y. Zoghbi, Department of Pediatrics, Program in Cell and Molec. Biology, Baylor College of Medicine, Houston, TX 77030, United States.
E-mail: hzoghbi@bcm.tmc.edu
SOURCE: Philosophical Transactions of the Royal Society of London Series B Biological Sciences, (29 JUN 1999), 354/1386 (1079-1081), 22 reference(s)
CODEN: PTRBAE ISSN: 0962-8436
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29477971 BIOTECHNO
AB Spinocerebellar ataxia type 1 (SCA1) is a dominantly inherited disorder characterized by progressive loss of coordination, motor impairment and the degeneration of cerebellar Purkinje cells, spinocerebellar tracts and brainstem nuclei. Many dominantly inherited neurodegenerative diseases share the mutational basis of SGA1: the expansion of a translated **CAG repeat** coding for glutamine. Mice lacking ataxin-I display learning deficits and altered hippocampal synaptic plasticity but none of the abnormalities seen in human SCA1; mice expressing ataxin-1 with an expanded CAG tract (82 glutamine residues), however, develop Purkinje cell pathology and ataxia. These results suggest that mutant ataxin-1 gains a novel function that leads to neuronal degeneration. This novel function might involve aberrant interaction(s) with cell-specific protein(s), which in turn might explain the selective neuronal pathology. Mutant ataxin-1 interacts preferentially with a leucine-rich acidic

nuclear protein that is abundantly expressed in cerebellar Purkinje cells and other brain regions affected in SCA1. Immunolocalization studies in affected neurons of patients and SCA1 transgenic mice showed that mutant ataxin-1 localizes to a single, ubiquitin-positive nuclear inclusion (NI) that alters the distribution of the proteasome and certain chaperones. Further analysis of NIs in transfected HeLa cells established that the proteasome and chaperone proteins co-localize with ataxin-1 **aggregates**. Moreover, overexpression of the chaperone HDJ-2/HSDJ in HeLa cells decreased ataxin-1 aggregation, suggesting that protein misfolding might underlie NI formation. To assess the importance of the nuclear localization of ataxin-1 and its role in SCA1 pathogenesis, two lines of transgenic mice were generated. In the first line, the nuclear localization signal was mutated so that full-**length** mutant ataxin-1 would remain in the cytoplasm; mice from this line did not develop any ataxia or pathology. This suggests that mutant ataxin-1 is pathogenic only in the nucleus. To assess the role of the **aggregates**, transgenic mice were generated with mutant ataxin-1 without the self-association domain (SAD) essential for **aggregate** formation. These mice developed ataxia and Purkinje cell abnormalities similar to those seen in SCA1 transgenic mice carrying full-**length** mutant ataxin-1, but lacked NIs. The nuclear milieu is thus a critical factor in SCA1 pathogenesis, but large NIs are not needed to initiate pathogenesis. They might instead be downstream of the primary pathogenic steps. Given the accumulated evidence, we propose the following model for SCA1 pathogenesis: expansion of the **polyglutamine** tract alters the conformation of ataxin-1, causing it to misfold. This in turn leads to aberrant protein interactions. Cell specificity is determined by the cell-specific proteins interacting with ataxin-1. Submicroscopic protein aggregation might occur because of protein misfolding, and those **aggregates** become detectable as NIs as the disease advances. Proteasome redistribution to the NI might contribute to disease progression by disturbing proteolysis and subsequent vital cellular functions.

L82 ANSWER 16 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29477965 BIOTECHNO
TITLE: Transgenic mice expressing mutated full-**length** HD cDNA: A paradigm for locomotor changes and selective neuronal loss in Huntington's disease
AUTHOR: Ready P.H.; Charles V.; Williams M.; Miller G.; Whetsell W.O. Jr.; Tagle D.A.
CORPORATE SOURCE: D.A. Tagle, Genetics and Molec. Biology Branch, Natl. Human Genome Resources Inst., National Institutes of Health, 49 Convent Drive, Bethesda, MD 20892, United States.
E-mail: datagle@helix.nih.gov
SOURCE: Philosophical Transactions of the Royal Society of London Series B Biological Sciences, (29 JUN 1999), 354/1386 (1035-1045), 58 reference(s)
CODEN: PTRBAE ISSN: 0962-8436
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29477965 BIOTECHNO
AB Huntington's disease (HD) is a progressive neurodegenerative disorder characterized clinically by motor and psychiatric disturbances and pathologically by neuronal loss and gliosis (reactive astrocytosis) particularly in the striatum and cerebral cortex. We have recently created HD full-**length** cDNA transgenic mouse models that may serve as a paradigm for HD. A more detailed characterization of these models is presented here. The transgene encoding normal huntingtin consists of 9417 bp of the huntingtin coding sequences including 16

tandem CAGs coding for **polyglutamines** as part of exon 1. The transgene is driven by a heterologous cytomegalovirus promoter. Five independent transgenic mouse lines were obtained using this construct. An additional six transgenic lines were obtained using full-**length** HD constructs that have been modified to include either 48 or 89 **CAG repeat** expansions. Southern blot and densitometric analyses indicated unique integration sites for the transgene in each of the lines with a copy number ranging from two to 22 copies. Widespread expression of the transgene in brain, heart, spleen, kidney, lung, liver and gonads from each line was determined by Western blot analyses. In the brain, transgene expression was found in cerebral cortex, striatum, hippocampus and cerebellum. Expression of the transgene was as much as five times the endogenous mouse huntingtin level. Phenotypically, only mice expressing 48 or 89 **CAG repeats** manifested progressive behavioural and motor dysfunction. Early behavioural abnormalities were characterized by trunk curling and clasping of both fore- and hindlimbs when the animals were suspended by their tails. Subsequently, these mice exhibited hyperkinetic movements, including heightened exploratory activities, unidirectional rotational behaviour, backflipping and excessive grooming that lasted for several weeks. Eventually, the animals progressed to a hypokinetic phase consisting of slowed movements and lack of response to sensory stimuli. Urine retention or incontinence was also a prominent feature of the hypokinetic phase. At the end stage of the disease process, HD48(B,D) and HD89 (A-C) mice became akinetic just prior to death. Neuropathological examination of mice at various stages indicated that it was only during the hypokinetic phase and thereafter when selective neuronal loss was most apparent. Regions of neurodegeneration and loss included the striatum, cerebral cortex, thalamus and hippocampus. TUNEL staining indicated an apoptotic mode of cell death in these brain regions. Comparative neuronal counts after Nissl staining showed as much as 20% loss of small and medium neurons in the striatum in mice at the hypokinetic and akinetic stages. Reactive astrocytosis accompanied the areas of neurodegeneration and loss. **Polyglutamine aggregates** in the form of neuronal intranuclear inclusions and diffuse nuclear and perinuclear aggregations were found in a small percentage of neurons, including those in brain regions that are typically spared in HD. This observation suggests that **polyglutamine aggregates** may not be sufficient to cause neuronal loss in HD. In both behavioural and neuropathological analyses, wild-type and transgenic animals with 16 **CAG repeats** were indistinguishable from each other and do not exhibit the changes observed for mice carrying the 48 and 89 **CAG repeat** mutations. Thus, animals expressing the **CAG repeat** expansions appear to represent clinically analogous models for HD pathogenesis, and may also provide insights into the underlying pathophysiological mechanisms of other triplet repeat disorders.

L82 ANSWER 17 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29328986 BIOTECHNO
TITLE: Abundant expression and cytoplasmic aggregations of α1A voltage-dependent calcium channel protein associated with neurodegeneration in spinocerebellar ataxia type 6
AUTHOR: Ishikawa K.; Fujigasaki H.; Saegusa H.; Ohwada K.; Fujita T.; Iwamoto H.; Komatsuzaki Y.; Toru S.; Toriyama H.; Watanabe M.; Ohkoshi N.; Shoji S.; Kanazawa I.; Tanabe T.; Mizusawa H.
CORPORATE SOURCE: H. Mizusawa, Department of Neurology, Tokyo Medical and Dental University, Yushima 1-5-45, Bunkyo-ku, 113-8519 Tokyo, Japan.
E-mail: h-mizusawa.nuro@med.tmd.ac.jp
SOURCE: Human Molecular Genetics, (1999), 8/7 (1185-1193), 42

reference(s)
CODEN: HMGEE5 ISSN: 0964-6906
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29328986 BIOTECHNO
AB Spinocerebellar ataxia type 6 (SCA6) is one of the eight neurodegenerative diseases caused by a trinucleotide (**CAG**) **repeat** expansion coding **polyglutamine** (**CAG repeat/polyglutamine** diseases) and is characterized by late onset autosomal dominant cerebellar ataxia and predominant loss of cerebellar Purkinje cells. Although the causative, small and stable **CAG repeat** expansion for this disease has been identified in the α1A voltage-dependent calcium channel gene (CACNA1A), the mechanism which leads to predominant Purkinje cell degeneration is totally unknown. In this study, we show that the calcium channel mRNA/protein containing the **CAG repeat/ polyglutamine** tract is most intensely expressed in Purkinje cells of human brains. In SCA6 brains, numerous oval or rod-shaped **aggregates** were seen exclusively in the cytoplasm of Purkinje cells. These cytoplasmic inclusions were not ubiquitinated, which contrasts with the neuronal intranuclear inclusions of other **CAG repeat/polyglutamine** diseases. In cultured cells, formation of perinuclear **aggregates** of the channel protein and apoptotic cell death were seen when transfected with full-**length** CACNA1A coding an expanded **polyglutamine** tract. The present study indicates that the mechanism of neurodegeneration in SCA6 is associated with cytoplasmic aggregations of the α1A calcium channel protein caused by a small **CAG repeat/ polyglutamine** expansion in CACNA1A.

L82 ANSWER 18 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29250887 BIOTECHNO
TITLE: Adenovirus-mediated expression of mutant DRPLA proteins with expanded **polyglutamine** stretches in neuronally differentiated PC12 cells. Preferential intranuclear **aggregate** formation and apoptosis
AUTHOR: Sato A.; Shimohata T.; Koide R.; Takano H.; Sato T.; Oyake M.; Igarashi S.; Tanaka K.; Inuzuka T.; Nawa H.; Tsuji S.
CORPORATE SOURCE: S. Tsuji, Department of Neurology, Brain Research Institute, Niigata University, 1-757 Asahimachi, Niigata 951-8585, Japan.
E-mail: tsuji@cc.niigata-u.ac.jp
SOURCE: Human Molecular Genetics, (1999), 8/6 (997-1006), 39 reference(s)
CODEN: HMGEE5 ISSN: 0964-6906
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29250887 BIOTECHNO
AB To investigate the molecular mechanisms of neurodegeneration caused by expanded **CAG repeats** in dentatorubral-pallidoluysian atrophy (DRPLA), an autosomal dominant neurodegenerative disorder caused by unstable expansion of a CAG trinucleotide repeat in the DRPLA gene on 12p13,31, we established an efficient expression system for truncated and full-**length** DRPLA proteins with normal or expanded **polyglutamine** stretches in neuronally differentiated PC12 cells and fibroblasts using an adenovirus expression system. Although **aggregate** body formation was observed both in neuronally

differentiated PC12 cells and in fibroblasts expressing truncated DRPLA proteins with Q82, > 97% (n = 3) of neuronally differentiated PC12 cells showed intranuclear inclusions, while only 31 ± 21% (n = 3) of fibroblasts had intranuclear inclusions at 3 days after infection. The percentage of apoptotic cells was significantly higher in neuronally differentiated PC12 cells expressing the truncated DRPLA protein with Q82 than in fibroblasts, suggesting the possibility that intranuclear **aggregate** bodies are formed preferentially in neuronally differentiated PC12 cells and that these cells are more vulnerable than fibroblasts to the toxic effects of expanded **polyglutamine** stretches in the DRPLA protein. When the full-**length** DRPLA protein with Q82 was expressed, **aggregate** bodies were found exclusively in the nuclei of the neuronally differentiated PC12 cells, while they were found in the cytoplasm of fibroblasts. Despite the presence of **aggregate** bodies, apoptosis was not induced by expression of the full-**length** DRPLA protein with Q82 in either neuronally differentiated PC12 cells or fibroblasts, suggesting that the presence of intranuclear **aggregate** bodies is in itself not necessarily toxic to cells.

L82 ANSWER 19 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29238182 BIOTECHNO
TITLE: Localization of rabbit huntingtin using a new panel of monoclonal antibodies
AUTHOR: Wilkinson F.L.; Man N.T.; Manilal S.B.; Thomas P.; Neal J.W.; Harper P.S.; Jones A.L.; Morris G.E.
CORPORATE SOURCE: G.E. Morris, MRIC Biochemistry Group, NE Wales Institute, Plas Coch, Wrexham LL11 2AW, United Kingdom.
E-mail: morrisge@newi.ac.uk
SOURCE: Molecular Brain Research, (1999), 69/1 (10-20), 41 reference(s)
CODEN: MBREE4 ISSN: 0169-328X
PUBLISHER ITEM IDENT.: S0169328X99000972
DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29238182 BIOTECHNO
AB Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by the expansion of a **CAG repeat** which is expressed as a **polyglutamine** tract near the N-terminus of the gene product, huntingtin. N-terminal huntingtin fragments form intranuclear **aggregates** in HD patients and these may be involved in the pathogenesis. Monoclonal antibodies (mAbs) against three different regions of huntingtin (amino acids 997-1276, 1844-2131 and 2703-2911) have been produced and two of the epitopes have been identified using phage displayed peptide libraries. All mAbs reacted with 350 kDa huntingtin on Western blots and one mAb from each region was selected for further study by strong immunoreactivity with neurons in different regions of rabbit brain and by ability to immunoprecipitate native huntingtin. Subcellular fractionation and sucrose density centrifugation of rabbit brain extract showed that most of the huntingtin exists as a high molecular weight complex in the cytoplasm. Two outstanding problems have been addressed; the location of huntingtin in tissues outside the central nervous system and whether huntingtin is present in the nucleus of normal cells. We conclude that huntingtin is present at low levels in most non-neuronal cells though we have identified an interstitial cell type in skin with very high immunoreactivity. Using both immunolocalization and nuclear purification methods, we were unable to exclude the possibility that a small proportion of full-**length** huntingtin is present in the nucleus.

L82 ANSWER 20 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29164670 BIOTECHNO
TITLE: Cleavage of atrophin-1 at caspase site aspartic acid 109 modulates cytotoxicity
AUTHOR: Ellerby L.M.; Andrusiak R.L.; Wellington C.L.; Hackam A.S.; Propp S.S.; Wood J.D.; Sharp A.H.; Margolis R.L.; Ross C.A.; Salvesen G.S.; Hayden M.R.; Bredesen D.E.
CORPORATE SOURCE: D.E. Bredesen, Program on Aging, Burnham Institute, 10901 N. Torrey Pines Rd., San Diego, CA 92037, United States.
SOURCE: Journal of Biological Chemistry, (26 MAR 1999), 274/13 (8730-8736), 41 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29164670 BIOTECHNO
AB Dentatorubropallidoluysian atrophy (DRPLA) is one of eight autosomal dominant neurodegenerative disorders characterized by an abnormal **CAG repeat** expansion which results in the expression of a protein with a **polyglutamine** stretch of excessive **length**. We have reported recently that four of the gene products (hunting-tin, atrophin-1 (DRPLA), ataxin-3, and androgen receptor) associated with these open reading frame triplet repeat expansions are substrates for the cysteine protease cell death executioners, the caspases. This led us to hypothesize that caspase cleavage of these proteins may represent a common step in the pathogenesis of each of these four neurodegenerative diseases. Here we present evidence that caspase cleavage of atrophin-1 modulates cytotoxicity and **aggregate** formation. Cleavage of atrophin-1 at Asp.sup.1.sup.0.sup.9 by caspases is critical for cytotoxicity because a mutant atrophin-1 that is resistant to caspase cleavage is associated with significantly decreased toxicity. Further, the altered cellular localization within the nucleus and **aggregate** formation associated with the expanded form of atrophin-1 are completely suppressed by mutation of the caspase cleavage site at Asp.sup.1.sup.0.sup.9. These results provide support for the toxic fragment hypothesis whereby cleavage of atrophin-1 by caspases may be an important step in the pathogenesis of DRPLA. Therefore, inhibiting caspase cleavage of the **polyglutamine**-containing proteins may be a feasible therapeutic strategy to prevent cell death.

L82 ANSWER 21 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1999:29124713 BIOTECHNO
TITLE: Expanded **polyglutamine** domain proteins bind **neurofilament** and alter the **neurofilament** network
AUTHOR: Nagai Y.; Onodera O.; Chun J.; Strittmatter W.J.; Burke J.R.
CORPORATE SOURCE: J.R. Burke, Department of Medicine (Neurology), Deane Laboratory, Duke University Medical Center, Durham, NC 27710, United States.
E-mail: james.burke@duke.edu
SOURCE: Experimental Neurology, (1999), 155/2 (195-203), 50 reference(s)
CODEN: EXNEAC ISSN: 0014-4886
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29124713 BIOTECHNO

AB Eight inherited neurodegenerative diseases are caused by genes with expanded **CAG repeats** coding for **polyglutamine** domains in the disease- producing proteins. The mechanism by which this expanded **polyglutamine** domain causes neurodegenerative disease is unknown, but nuclear and cytoplasmic **polyglutamine** protein aggregation is a common feature. In transfected COS7 cells, expanded **polyglutamine** proteins **aggregate** and disrupt the vimentin intermediate filament network. Since neurons have an intermediate filament network composed of **neurofilament** (NF) and NF abnormalities occur in neurodegenerative diseases, we examined whether pathologic-**length polyglutamine** domain proteins also interact with NF. We expressed varying **lengths polyglutamine**-green fluorescent protein fusion proteins in a neuroblast cell line, TR1. Pathologic-**length polyglutamine**-GFP fusion proteins formed large cytoplasmic **aggregates** surrounded by **neurofilament**. Immunoisolation of pathologic-**length polyglutamine** proteins coisolated 68- kDa NF protein demonstrating molecular interaction. These observations suggest that **polyglutamine** interaction with NF is important in the pathogenesis of the **polyglutamine** repeat diseases.

L82 ANSWER 22 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1998:28221240 BIOTECHNO
TITLE: Truncated N-terminal fragments of huntingtin with expanded glutamine repeats form nuclear and cytoplasmic **aggregates** in cell culture
AUTHOR: Cooper J.K.; Schilling G.; Peters M.F.; Herring W.J.; Sharp A.H.; Kaminsky Z.; Masone J.; Khan F.A.; Delanoy M.; Borchelt D.R.; Dawson V.L.; Dawson T.M.; Ross C.A.
CORPORATE SOURCE: C.A. Ross, Laboratory of Molecular Neurobiology, Department of Psychiatry, Johns Hopkins Univ. School Medicine, 720 Rutland Avenue, Baltimore, MD 21205-2196, United States.
E-mail: caross@jhu.edu
SOURCE: Human Molecular Genetics, (1998), 7/5 (783-790), 40 reference(s)
CODEN: HMGEE5 ISSN: 0964-6906
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1998:28221240 BIOTECHNO
AB Huntington's disease (HD) is a progressive neurodegenerative disorder caused by an expanding **CAG repeat** coding for **polyglutamine** in the huntingtin protein. Recent data have suggested the possibility that an N-terminal fragment of huntingtin may **aggregate** in neurons of patients with HD, both in the cytoplasm, forming dystrophic neurites, and in the nucleus, forming intranuclear neuronal inclusion bodies. An animal model of HD using the short N-terminal fragment of huntingtin has also been found to have intranuclear inclusions and this same fragment can **aggregate** in vitro. We have now developed a cell culture model demonstrating that N-terminal fragments of huntingtin with expanded glutamine repeats **aggregate** both in the cytoplasm and in the nucleus. Neuroblastoma cells transiently transfected with full-**length** huntingtin constructs with either a normal or expanded repeat had diffuse cytoplasmic localization of the protein. In contrast, cells transfected with truncated N-terminal fragments showed aggregation only if the glutamine repeat was expanded. The **aggregates** were often ubiquitinated. The shorter truncated product appeared to form more **aggregates** in the nucleus. Cells transfected with the expanded repeat construct but not the normal repeat construct showed enhanced

toxicity to the apoptosis-inducing agent staurosporine. These data indicate that N-terminal truncated fragments of huntingtin with expanded glutamine repeats can **aggregate** in cells in culture and that this aggregation can be toxic to cells. This model will be useful for future experiments to test mechanisms of aggregation and toxicity and potentially for testing experimental therapeutic interventions.

L82 ANSWER 23 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1998:28082456 BIOTECHNO
TITLE: Suppression of **aggregate** formation and apoptosis by transglutaminase inhibitors in cells expressing truncated DRPLA protein with an expanded **polyglutamine** stretch
AUTHOR: Igarashi S.; Koide R.; Shimohata T.; Yamada M.; Hayashi Y.; Takano H.; Date H.; Oyake M.; Sato T.; Sato A.; Egawa S.; Ikeuchi T.; Tanaka H.; Nakano R.; Tanaka K.; Hozumi I.; Inuzuka T.; Takahashi H.; Tsuji S.
CORPORATE SOURCE: S. Tsuji, Department of Neurology, Niigata University, 1-757 Asahimachi, Niigata 951, Japan.
E-mail: tsuji@cc.niigata-u.ac.jp
SOURCE: Nature Genetics, (1998), 18/2 (111-117), 38 reference(s)
CODEN: NGENEC ISSN: 1061-4036
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1998:28082456 BIOTECHNO
AB To elucidate the molecular mechanisms whereby expanded **polyglutamine** stretches elicit a gain of toxic function, we expressed full-**length** and truncated DRPLA (dentatorubral-pallidoluysian atrophy) cDNAs with or without expanded **CAG repeats** in COS-7 cells. We found that truncated DRPLA proteins containing an expanded **polyglutamine** stretch form filamentous peri- and intranuclear **aggregates** and undergo apoptosis. The apoptotic cell death was partially suppressed by the transglutaminase inhibitors cystamine and monodansyl cadaverine (but not putrescine), suggesting involvement of a transglutaminase reaction and providing a potential basis for the development of therapeutic measures for **CAG-repeat** expansion diseases.

L82 ANSWER 24 OF 29 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1998:28040746 BIOTECHNO
TITLE: Truncated forms of the androgen receptor are associated with **polyglutamine** expansion in X-linked spinal and bulbar muscular atrophy
AUTHOR: Butler R.; Leigh P.N.; McPhaul M.J.; Gallo J.-M.
CORPORATE SOURCE: J.-M. Gallo, Department of Clinical Neurosciences, Institute of Psychiatry, King's College Sch. Med. Dentistry, De Crespigny Park, London SE5 8AF, United Kingdom.
E-mail: j.gallo@iop.bpmf.ac.uk
SOURCE: Human Molecular Genetics, (1998), 7/1 (121-127), 58 reference(s)
CODEN: HMGEE5 ISSN: 0964-6906
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1998:28040746 BIOTECHNO
AB X-linked spinal and bulbar muscular atrophy (SBMA) is a rare form of motor neuron degeneration linked to a **CAG repeat**

expansion in the first exon of the androgen receptor gene coding for a **polyglutamine** tract. In order to investigate the properties of the SBMA androgen receptor in neuronal cells, cDNAs coding for a wild-type (19 **CAG repeats**) and a SBMA mutant androgen receptor (52 **CAG repeats**) were transfected into mouse neuroblastoma NB2a/d1 cells. The full **length** androgen receptor proteins, of 110-112 kDa and 114-116 kDa for the wild-type and mutant protein, respectively, were detected by Western blotting in transfected cells. In addition, the presence of an expanded **polyglutamine** tract in the SBMA androgen receptor appears to enhance the production of C-terminally truncated fragments of the protein. A 74 kDa fragment was particularly prominent in cells expressing the SBMA androgen receptor. From its size, it can be deduced that the 74 kDa fragment lacks the hormone binding domain but retains the DNA binding domain. The 74 kDa fragment may therefore be toxic to motor neurons by initiating the transcription of specific genes in the absence of hormonal control. Immunofluorescence microscopy on transfected NB2a/d1 cells showed that, after hormone activation, the wild-type androgen receptor translocated to the nucleus whereas the SBMA androgen receptor was mainly localized in the cytoplasm in the form of dense **aggregates** with very little androgen receptor protein in the nucleus. This could explain the reduction in transcriptional activity of the SBMA mutant as compared with wild-type androgen receptor.

L82 ANSWER 25 OF 29 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2004:66339 LIFESCI
TITLE: Experimental Therapeutics in Transgenic Mouse Models of Huntington's Disease
AUTHOR: Beal, M. Flint; Ferrante, Robert J.
SOURCE: Nature Reviews: Neuroscience [Nat. Rev. Neurosci.], (20040505) vol. 5, no. 5, pp. 373-384. ISSN: 1471-0048.
DOCUMENT TYPE: Journal
TREATMENT CODE: General Review
FILE SEGMENT: N3
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Despite important advances in understanding and elucidating the molecular and mechanistic pathways that mediate progression in Huntington's disease (HD), effective pharmacotherapy remains elusive. Insights into disease pathogenesis have come from studies using tissue culture, yeast, Caenorhabditis elegans, Drosophila melanogaster and transgenic mouse models. Here, we present a brief overview of HD pathogenesis and discuss the efficacy of therapeutic agents in transgenic mouse models of HD. We conclude by considering issues that affect the translation of findings in transgenic mouse models of HD to human clinical trials. In Summary: Huntingtin is a predominantly cytoplasmic protein that is found in neurons throughout the brain. The precise mechanism by which mutant huntingtin causes Huntington's disease (HD) is unknown but seems to be gain-of-function. The gene that encodes this protein can be mutated by expansion of a trinucleotide **CAG repeat** that encodes glutamine. N-terminal fragments of mutant huntingtin form toxic protein **aggregates** in neurons. Mutant huntingtin causes progressive neuronal dysfunction and death: HD is ultimately lethal. There are several different transgenic mouse models of HD that have enhanced the study of this disorder and the capacity to test promising therapeutics. Mouse models fall into three categories: (1) those that express full-**length** mutant human huntingtin; (2) those that express fragments of the mutant human huntingtin gene; and (3) those with **CAG repeats** inserted into the murine huntingtin gene. These mouse models have been used to investigate the role in HD of several processes that might be targeted therapeutically. These processes include: proteolysis of huntingtin; aggregation of huntingtin; apoptosis;

transcriptional dysregulation; mitochondrial dysfunction; excitotoxicity; inflammation and oxidative damage; and transglutaminase activity. Vaccination against toxic proteins and transplantation of healthy brain tissue are two approaches to treatment that are under investigation. There is no consensus as to which type of mouse model is the best model of human HD. There have been few clinical trials of treatments in humans on which to base a comparative conclusion.

L82 ANSWER 26 OF 29 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2003:76759 LIFESCI
TITLE: Ataxin-1 Regulators in the Spotlight
AUTHOR: Heintz, N.
CORPORATE SOURCE: HHMI, Department of Molecular Biology, Rockefeller University, New York, NY 10021, USA; E-mail: heintz@rockefeller.edu
SOURCE: Science (Washington) [Science (Wash.)], (20030704) vol. 301, no. 5629, pp. 59-60.
ISSN: 0036-8075.
DOCUMENT TYPE: Journal
TREATMENT CODE: General Review
FILE SEGMENT: G; N3
LANGUAGE: English
AB The presence of aberrant protein **aggregates** in neurons is a shared feature of many human neurodegenerative diseases, including the "triplet repeat" disorders and Parkinson's and Alzheimer's diseases. The triplet repeat disorders--Huntington's disease, spinobulbar muscular atrophy (SBMA), and the spinocerebellar ataxias (SCA) 1, 2, 3, 6, 7, and 17--are caused by the expansion of a **CAG repeat** in the affected gene, which produces an aberrant protein carrying an expanded **polyglutamine** (polyQ) tract. Both the time of onset and severity of the triplet repeat diseases correlate with the **length** of the polyQ tract, and **aggregates** containing the polyQ protein are the pathological hallmark of these disorders.

L82 ANSWER 27 OF 29 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2003:45445 LIFESCI
TITLE: Amyloid-like Features of **Polyglutamine Aggregates** and Their Assembly Kinetics
AUTHOR: Chen, Songming; Berthelier, V.; Hamilton, J.B.; O'Nuallain, B.; Wetzel, R.
CORPORATE SOURCE: Graduate School of Medicine, University of Tennessee Medical Center, 1924 Alcoa Highway, Knoxville, TN 37920, USA
SOURCE: Biochemistry (Washington) [Biochemistry (Wash.)], (20020611) vol. 41, no. 23, pp. 7391-7399.
ISSN: 0006-2960.
DOCUMENT TYPE: Journal
FILE SEGMENT: N3
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The repeat **length**-dependent tendency of the **polyglutamine** sequences of certain proteins to form **aggregates** may underlie the cytotoxicity of these sequences in expanded **CAG repeat** diseases such as Huntington's disease. We report here a number of features of various **polyglutamine** (polyGln) **aggregates** and their assembly pathways that bear a resemblance to generally recognized defining features of amyloid fibrils. PolyGln aggregation kinetics displays concentration and **length** dependence and a lag phase that can be abbreviated by seeding. PolyGln **aggregates** exhibit classical beta -sheet-rich circular dichroism spectra consistent with an amyloid-like substructure. The fundamental structural unit of all the in vitro **aggregates** described here is a filament about 3 nm in width, resembling the

protofibrillar intermediates in amyloid fibril assembly. We observed these filamentous structures either as isolated threads, as components of ribbonlike sheets, or, rarely, in amyloid-like twisted fibrils. All of the polyGln **aggregates** described here bind thioflavin T and shift its fluorescence spectrum. Although all polyGln **aggregates** tested bind the dye Congo red, only **aggregates** of a relatively long polyGln peptide exhibit Congo red birefringence, and this birefringence is only observed in a small portion of these **aggregates**. Remarkably, a monoclonal antibody with high selectivity for a generic amyloid fibril conformational epitope is capable of binding polyGln **aggregates**. Thus, polyGln **aggregates** exhibit most of the characteristic features of amyloid, but the twisted fibril structure with Congo red birefringence is not the predominant form in the polyGln repeat **length** range studied here. We also find that polyGln peptides exhibit an unusual freezing-dependent aggregation that appears to be caused by the freeze concentration of peptide and/or buffer components. This is of both fundamental and practical significance. PolyGln aggregation is revealed to be a highly specific process consistent with a significant degree of order in the molecular structure of the product. This ordered structure, or the assembly process leading to it, may be responsible for the cell-specific neuronal degeneration observed in Huntington's and other expanded **CAG repeat** diseases.

L82 ANSWER 28 OF 29 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2003:26757 LIFESCI
TITLE: Pivotal role of oligomerization in expanded **polyglutamine** neurodegenerative disorders
AUTHOR: Sanchez, I.; Mahlke, C.; Yuan, J.
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA; E-mail: Junying_Yuan@hms.harvard.edu
SOURCE: Nature, (20030123) vol. 421, no. 6921, pp. 373-379. ISSN: 0028-0836.
DOCUMENT TYPE: Journal
FILE SEGMENT: N3; G
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The expansion of a **CAG repeat** coding for **polyglutamine** in otherwise unrelated gene products is central to eight neurodegenerative disorders including Huntington's disease. It has been well documented that expanded **polyglutamine** fragments, cleaved from their respective full-**length** proteins, form microscopically visible **aggregates** in affected individuals and in transgenic mice. The contribution of **polyglutamine** oligomers to neurodegeneration, however, is controversial. The azo-dye Congo red binds preferentially to [beta]-sheets containing amyloid fibrils and can specifically inhibit oligomerization and disrupt preformed oligomers. Here we show that inhibition of **polyglutamine** oligomerization by Congo red prevents ATP depletion and caspase activation, preserves normal cellular protein synthesis and degradation functions, and promotes the clearance of expanded **polyglutamine** repeats in vivo and in vitro. Infusion of Congo red into a transgenic mouse model of Huntington's disease, well after the onset of symptoms, promotes the clearance of expanded repeats in vivo and exerts marked protective effects on survival, weight loss and motor function. We conclude that oligomerization is a crucial determinant in the biochemical properties of expanded **polyglutamine** that are central to their chronic cytotoxicity.

L82 ANSWER 29 OF 29 LIFESCI COPYRIGHT 2005 CSA on STN
ACCESSION NUMBER: 2000:84117 LIFESCI
TITLE: **Polyglutamine**-Induced Ion Channels: A Possible Mechanism for the Neurotoxicity of Huntington and Other **CAG Repeat** Diseases

AUTHOR: Hirakura, Yutaka; Azimov, R.; Azimova, R.; Kagan, B.L.
CORPORATE SOURCE: Rm. C8-849 NPI, Westwood Plaza, Los Angeles, CA 90024, USA; E-mail: bkagan@mednet.ucla.edu
SOURCE: Journal of Neuroscience Research [J. Neurosci. Res.], (20000515) vol. 60, no. 4, pp. 490-494.
ISSN: 0360-4012.
DOCUMENT TYPE: Journal
FILE SEGMENT: N3
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **CAG repeats** resulting in long **polyglutamine** tracts have been implicated in the pathogenesis of at least eight neurodegenerative diseases including Huntington. Expression of **polyglutamine** repeats is required for disease and increasing **length** of the repeats leads to earlier onset of illness (anticipation). Expression of **polyglutamine** repeats in cultured neurons leads to deposition of intracellular **aggregates** resembling those found in amyloid diseases, and to neurotoxicity. We report here that **polyglutamine** can induce large (19-220 pS), long-lived, (lifetime = 6 sec), non-selective (P sub(cation) = P sub(anion)) ion channels in planar phospholipid bilayer membranes, and that channel formation is enhanced by acidic pH. We propose that channel formation may be a mechanism of cellular toxicity in Huntington and other **CAG repeat** disease.